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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02079648.8

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R C van Dijk

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Non-steroidal androgen compounds

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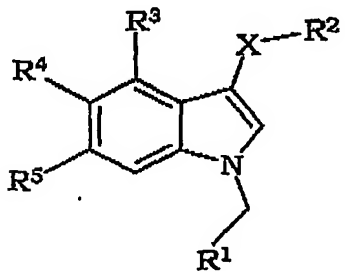
NON-STEROIDAL ANDROGEN COMPOUNDS

The invention relates to indole derivatives, their preparation and their use for the treatment of androgen-receptor related conditions, disorders or diseases.

Compounds possessing androgenic activity are useful in the treatment of men with low endogenous levels of circulating androgenic hormones or men with suppressed androgenic effects. Such treatments are prescribed to older men, to hypogonadal men or men treated with progestagens for male contraception. In addition, potent androgens suppress spermatogenesis and can be used as male contraceptives.

It is thus important to obtain compounds with high affinity for the androgen receptor. Non-steroidal compounds with high affinity for the androgen receptor are particularly useful since they have different tissue distribution characteristics than steroidal androgens and can be designed by proper choice of substituents to be more or less selective for certain tissues. For example, an action in the brain is usually prevented when compounds are strongly hydrophilic or carry an ionic charge.

The subject invention provides non-steroidal compounds with affinity for the androgen receptor. These compounds are useful for the treatment of androgen-receptor related disorders. The compounds of the subject invention have a structure according to formula I:



wherein

X is S, SO or SO_2;

R^1 is a 5-6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from

the group consisting of halogen, CN, (1C-4C)fluoroalkyl, nitro, (1C-4C)alkyl, (1C-4C)alkyloxy or (1C-4C)fluoroalkoxy;

R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, 2-pyridyl, 2-pyridyl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl;

R^3 is H, halogen or (1C-4C)alkyl;

R^4 is H, OH or halogen;

R^5 is H, OH, (1C-4C)alkoxy, NH_2, CN, halogen, (1C-4C)fluoroalkyl, NO_2, hydroxy(1C-4C)alkyl, CO_2H, NHR^6 or $C(O)N(R^8,R^9)$. Herein is R^6 (1C-6C)acyl optionally substituted with one or more halogens, and are R^8 and R^9 each independently H, (1C-6C)cycloalkyl, CH_2R^{10} or form together with the N a heterocyclic 5-6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl, where by R^{10} is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)amino, (mono- or di(1C-4C)alkyl)aminocarbonyl, or a 5-6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring.

In one embodiment R^1 is a 5-6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, CF_3, nitro, methoxy, trifluoromethoxy or methyl; and R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, 2-pyridyl, 2-pyridyl-N-oxide, benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl; and R^3 is H, halogen or (1C-2C)alkyl; and R^4 is H or F.

In another embodiment R^5 is H, (1C-4C)alkoxy, CN, Hal, (1C-4C)fluoroalkyl, NO_2, or R^5 is NHR^6, wherein R^6 is (1C-6C)acyl optionally substituted with one or more halogens, or R^5 is $C(O)N(R^8,R^9)$, wherein R^8 and R^9 each independently are H, (1C-6C)cycloalkyl, or R^8 and R^9 form together with the N a heterocyclic 5-6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl, or R^8 and R^9 each independently are CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)amino, (mono- or di(1C-4C)alkyl)-aminocarbonyl, or a 5-6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring.

In yet another embodiment R^3 is H or halogen; R^4 being H; and R^5 being H, OH, (1C-4C)alkyloxy, CN, F, Cl, CF_3, NO_2, or R^5 is NHR^6, wherein R^6 is (1C-3C)acyl optionally substituted with one or more halogens, or R^5 is $C(O)N(R^8,R^9)$, wherein R^8 and R^9 each

independently are H, (1C-4C)cycloalkyl, or R^8 and R^9 each independently are CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, (1C-2C)alkylester of carboxy(1C-2C)alkyl, (1C-3C)alkyloxy(1C-3C)alkyl), (1C-4C)cycloalkyl, (mono- or di(1C-4C)alkyl)amino, (mono- or di(1C-4C)alkyl)aminocarbonyl, or a 5-membered heterocyclic ring.

In another embodiment, X is S or SO_2; R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-benzamide, 2-methoxyphenyl, 2-cyanophenyl or 2-pyridyl; R^3 is H or F; R^5 is H, OH, (1C-2C)alkyloxy, CN, F, Cl, CF_3, NO_2, or R^5 is NHR^6, wherein R^6 is acetyl or trifluoroacetyl, or R^5 is $C(O)N(R^8,R^9)$, wherein R^8 is H and R^9 is H, cyclopropyl or R^9 is CH_2R^{10}, wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, methoxy(1C-2C)alkyl, cyclopropyl.

In those cases that a compound of the invention contains a basic amine function, the compound may be used as a free base or as a pharmaceutically acceptable salt such as hydrochloride, acetate, oxalate, tartrate, citrate, phosphate, maleate or fumarate.

A compound according to the invention is a compound as defined above, a salt thereof, a hydrate thereof or a prodrug thereof.

The terms used in this description have the following meaning:
alkyl is a branched or unbranched alkyl group, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, hexyl, octyl, capryl, or lauryl;
alkenyl is a branched or unbranched alkenyl group, such as ethenyl, 2-butenyl, etc.;
alkynyl is a branched or unbranched alkynyl group, such as ethynyl and propynyl;
aryl is a mono- or polycyclic, homo- or heterocyclic aromatic ring system, such as phenyl, naphtyl or pyridinyl; a monocyclic ring with 6 atoms is preferred for use;
aroyl is arylcarbonyl such as a benzoyl group;
alkanoyl means a formyl or alkylcarbonyl group such as formyl, acetyl and propanoyl;
acyl is a (substituent-)carbonyl group, such as an aroyl or alkanoyl;
carboxyl is a –COOH substituent, making the compound an organic acid;
carboxylate is a salt of a carboxyl substituent.
cycloalkyl is a cyclized unbranched alkyl group, such as cyclopropyl, cyclopentyl;
The prefixes (1C-4C), (2C-4C) etc. have the usual meaning to restrict the meaning of the indicated group to those with 1 to 4, 2 to 4 etc. carbon atoms;
halogen refers to fluorine, chlorine, bromine and iodine.

The androgen receptor affinity and efficacy of the compounds according to the invention makes them suitable for use in the treatment of androgen-receptor related disorders and in diagnostic methods focussed on the amount and/or location of androgen receptors in various tissues. For the latter purpose it can be preferred to make labelled variants of the compounds according to the invention. Typical androgen receptor-related treatments are those for male contraception and male or female hormone replacement therapy. Thus the invention also pertains to a method of treatment of androgen insufficiency, by administering to a male or female human or animal an effective amount of any of the above compounds. The subject invention also lies in the use of any of its compounds for the preparation of a medicine for treating androgen insufficiency. In the context of the invention, the term "androgen insufficiency" is to be understood to pertain to all kinds of diseases, disorders, and symptoms in which a male or a female suffers from too low a testosterone level, such as in hypogonadal men. In particular, the androgen insufficiency to be treated by a compound of the invention is the reduction of the testosterone level which a male individual incurs as a result of age (the compound of the invention is then used for male hormone replacement therapy), or when he is subject to male contraception. In the context of male contraception, the compound of the invention especially serves to neutralise the effect of regimens of male hormone contraception in which a sterilitant such as a progestagen or LHRH (luteinizing hormone releasing hormone) is administered regularly, *e.g.* daily, or it is used as the sole male contraceptive substance.

The compounds of the invention can be produced by various methods known in the art of organic chemistry in general. More specifically the routes of synthesis as illustrated in the following schemes and examples can be used. In the schemes and examples the following abbreviations were used:

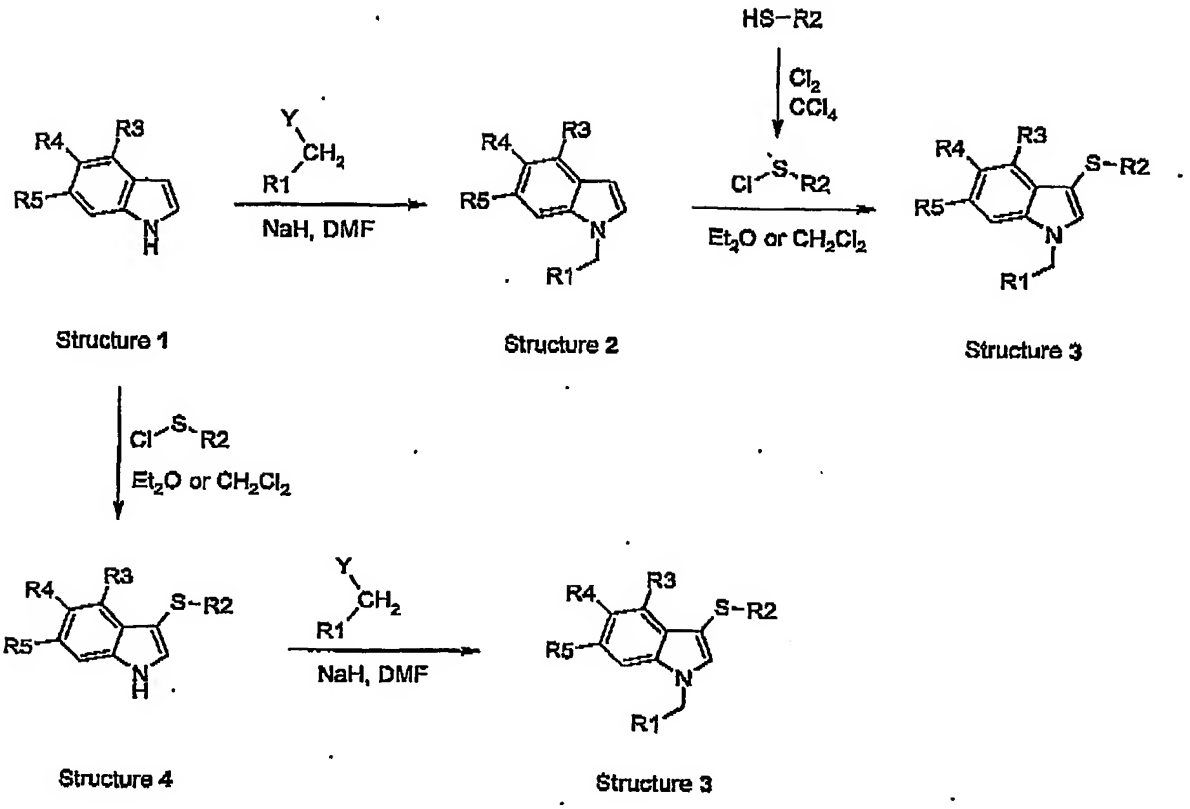
DMF = dimethylformamide
mCPBA = *meta* chloro perbenzoic acid
THF = tetrahydofuran
TBTU = 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
DIPEA = diisopropylethylamine
EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBt = 1-hydroxybenzotriazole
NMM = N-methylmorpholine
SPE = solid phase extraction

RP-SPE = reversed phase solid phase extraction
DMSO = dimethylsulfoxide
DCM = dichloromethane
DHT = 5α-dihydrotestosterone

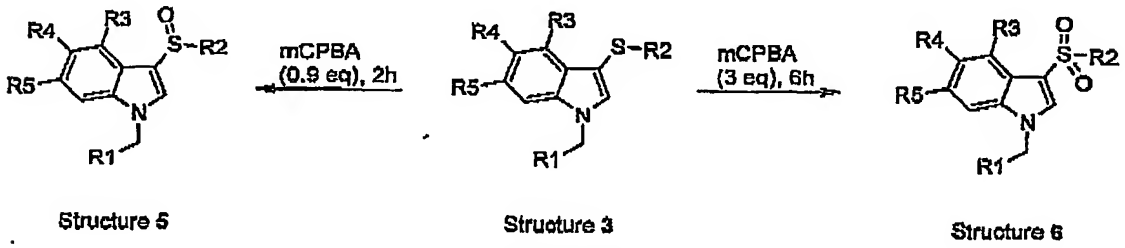
In each of the Schemes I-V the meanings of the symbols correspond to the definitions given in the previous paragraphs.

Substituted indole compounds of structure 3 were prepared in two steps from the correctly substituted indoles of structure 1, via two different routes. In the first route a correctly substituted indole of structure 1 is N-alkylated with a halide of type R^1CH_2Y, where Y is a halogen, with NaH as a base in DMF at 0°C to room temperature, to give a compound of structure 2. Structure 2 is then sulfenylated at the C-3 position of the indole ring by reaction with a sulfenyl chloride in either CH_2Cl_2 or diethyl ether at room temperature, to give structure 3. In the second route the two steps of the first route are reversed: the correctly substituted indole of structure 1 is first sulfenylated at the C-3 position of the indole to give structure 4, followed by N-alkylation with R^1CH_2Y to give structure 3 (Scheme I).

Scheme I

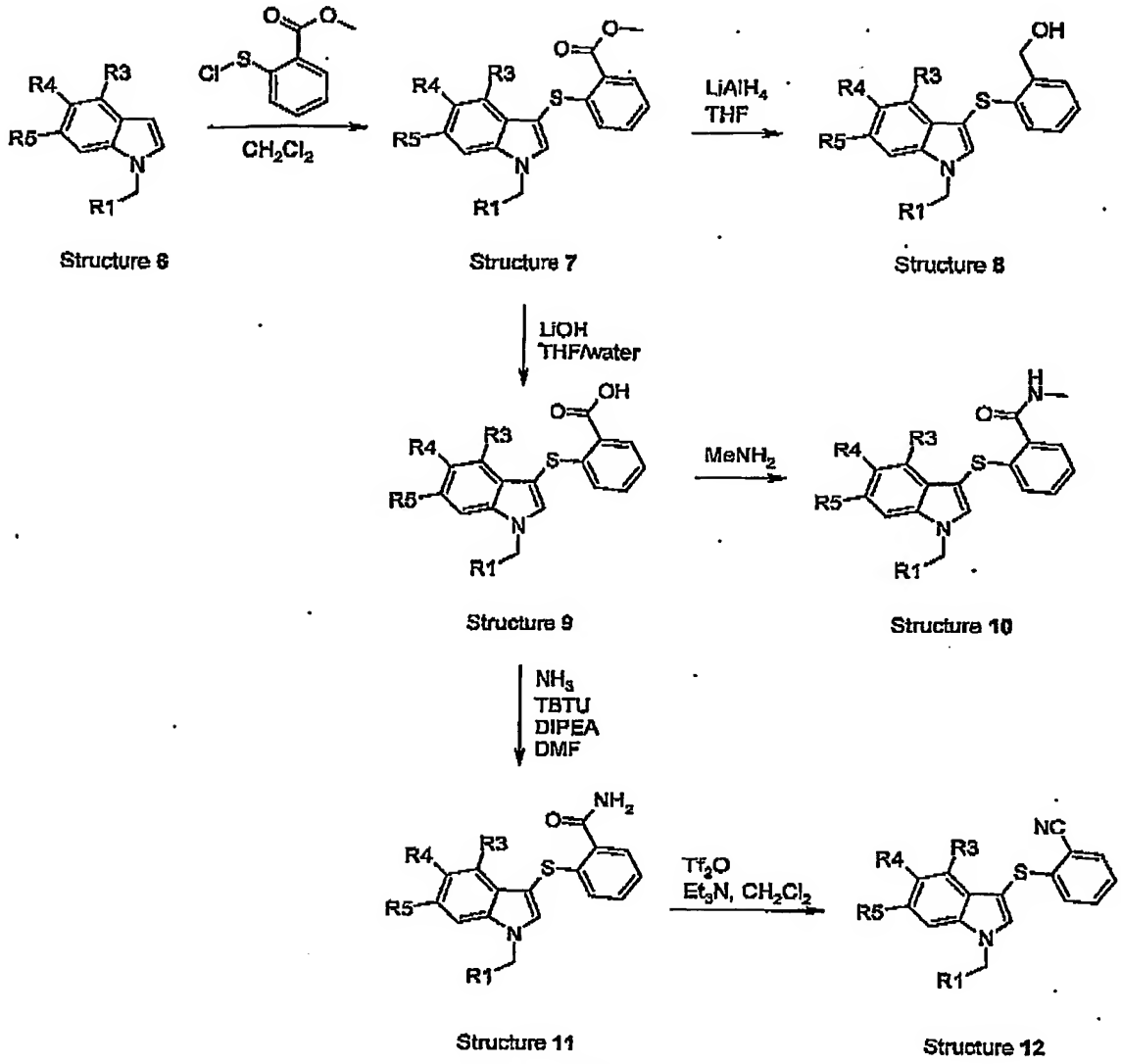


Sulfoxides of structure **5** can be obtained by oxidation of the corresponding sulfide (Structure **3**) by reaction with 0.9 equivalents of mCPBA. Sulfones of structure **6** can be obtained by oxidation of the corresponding sulfide (Structure **3**) by reaction with 3 equivalents of mCPBA (Scheme **II**).



Scheme II

Scheme **III** describes the synthesis of compounds of structure **3**, in which the R^2 group is a phenyl ring substituted on the 2-position with either CO_2Me (Structure **7**), CH_2OH (Structure **8**), CO_2H (Structure **9**), CONHMe (Structure **10**), $CONH_2$ (Structure **11**) or CN (Structure **12**).



Structure 6 Structure 7 Structure 8

Structure 9 Structure 10

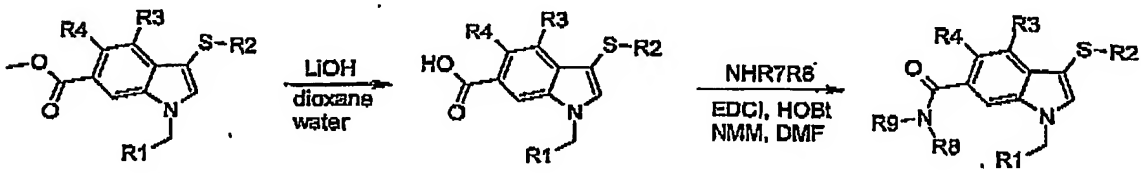
Structure 11 Structure 12

Scheme III

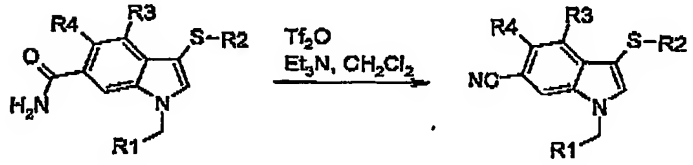
In the first step a substituted indole of structure **6** is sulfenylated at the 3-position with 2-(carboxymethyl)-phenylsulfenyl chloride, which was prepared from methylthiosalicylate and chlorine gas, to give a compound of structure **7**. Reduction of the methyl ester moiety of compounds of structure **7** with $LiAlH_4$ gave the corresponding hydroxymethyl compounds of structure **8**. Saponification of the methyl ester moiety of compounds of structure **7** with lithium hydroxide gave the corresponding carboxylic acid compounds of structure **9**. The carboxylic acid moiety of

compounds of structure 9 can be converted to the corresponding carboxamide by reaction with an amine, TBTU and DIPEA in DMF at room temperature. By this method structure 10 was obtained when methylamine was used as the amine and structure 11 was obtained when NH_3 was used as the amine. Dehydration of the benzamide moiety of structure 11 with Tf_2O and triethylamine in CH_2Cl_2 afforded the corresponding benzonitrile compound of structure 12 (Scheme III).

Scheme IV



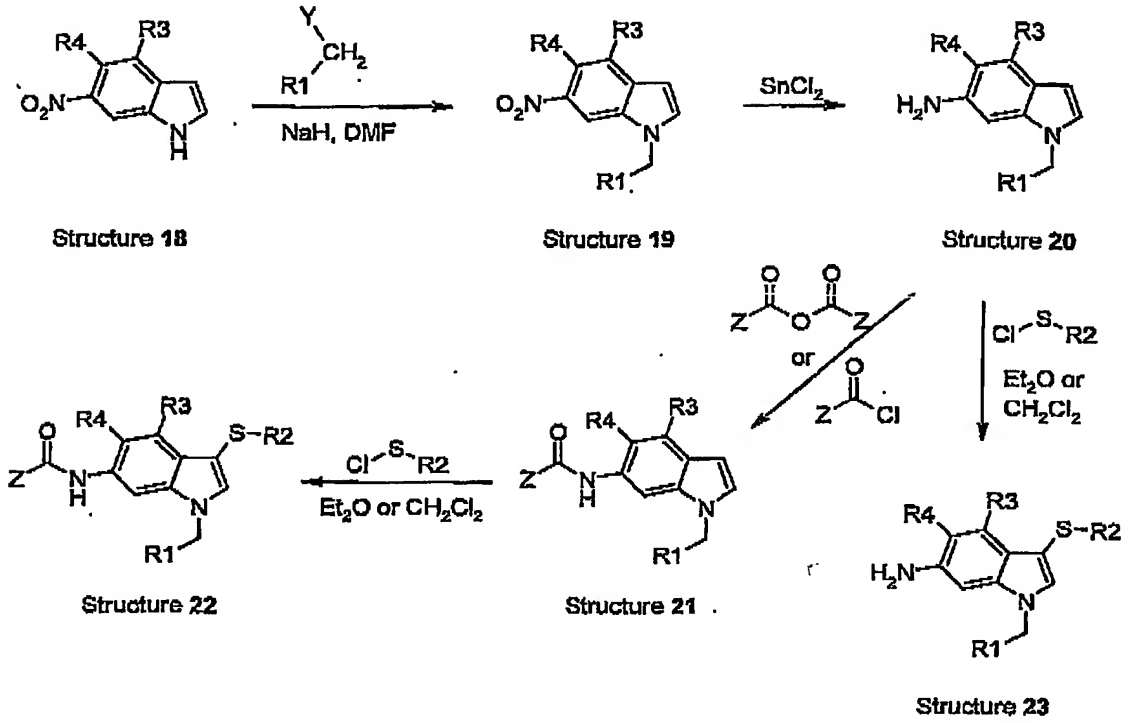
Structure 13 Structure 14 Structure 15



Structure 16 Structure 17

Scheme IV describes the synthesis of compounds of structure 3, in which the indole ring is substituted at the 6-position with either CO_2Me (Structure 13), CO_2H (Structure 14), $CONR^8R^9$ (Structure 15), $CONH_2$ (Structure 16) or CN (Structure 17). Saponification of the methyl ester moiety of structure 13 with lithium hydroxide afforded the corresponding carboxylic acid of structure 14. The carboxylic acid moiety of structure 14 can be converted to the corresponding carboxamides of structures 15 and 16 by reaction with an amine or amine salt, in the presence of EDCI and HOBt in a mixture of NMM and DMF at room temperature. Dehydration of the benzamide moiety of structure 16 with Tf_2O and triethylamine in CH_2Cl_2 afforded the corresponding benzonitrile compound of structure 17 (Scheme IV).

Scheme V



Scheme V describes the synthesis of compounds of structure 22 containing an acylated amine functionality on the 6-position of the indole ring. These compounds can be synthesised from 6-nitro indoles of structure 18 in 4 steps. In the first step the indole of structure 18 is alkylated on the nitrogen atom by reaction of a halide of type R^1CH_2Y, in which Y is halogen, with NaH as a base in DMF to give compounds of structure 19. In the second step the nitro group of structure 19 is reduced to an amine group by $SnCl_2$ to give structure 20. Subsequent acylation of the amine group with an acid chloride of type ZCOCl afforded structure 21, which was then sulfenylated at the 3-position of the indole ring by reaction with a sulfenyl chloride in either CH_2Cl_2 or Et_2O as a solvent, at room temperature, to give compounds of structure 22. Direct sulfenylation of a compound of structure 20 with a sulfenyl chloride afforded structure 23.

The present invention also relates to a pharmaceutical composition comprising the non-steroidal compound according to the invention mixed with a pharmaceutically acceptable auxiliary, such as described in the standard reference Gennaro *et al*, *Remmington: The Science and Practice of Pharmacy*, (20th ed., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing). Suitable auxiliaries are made available in e.g. the Handbook of Pharmaceutical Excipients (2nd Edition, Editors A. Wade and P.J. Weller; American Pharmaceutical Association;

Washington; The Pharmaceutical Press; London, 1994). The mixture of a compound according to the invention and a pharmaceutically acceptable auxiliary may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. nasal spray. For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. The compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and any other preparation for sustained release.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

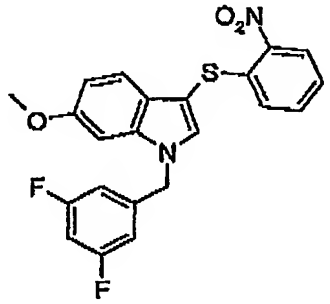
The dosage amounts of the present compounds will be of the normal order for pharmaceutically active compounds, e.g. of the order of 0.001 to 50 mg/kg body weight of the recipient per administration. The recipient can be a human or an animal in need of an androgen receptor-related treatment.

The invention is illustrated by the following examples.

Examples

Example 1

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (Compound 63, Structure 3 of Scheme I, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)



General method 1: N-alkylation of a (un)substituted indole of structure **1** to give N-alkylated indole of structure **2**, followed by 3-sulfenylation to give substituted indoles of structure **3** (Scheme I).

(a) 1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indole (Structure 2 of Scheme I, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

Under a nitrogen atmosphere: to a cooled (0°C) solution of 6-methoxyindole (863 mg, 5.86 mmol) in DMF (40 mL) was added NaH (60% in oil; 281 mg, 7.03 mmol) in small portions over a 3 minute period. The resulting green suspension was stirred at 0°C for 10 min. Then 3,5-difluorobenzyl bromide (0.91 mL, 7.03 mmol) was added. The mixture was stirred at 0°C for 1 h and then at room temperature for another 21 h. Ethyl acetate (50 mL) was added and the mixture was washed with 3% aqueous citric acid (3x50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a green oil (1.43 g). The crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:9) to give the title compound as a colourless oil (1.23 g, yield = 77%).

LCMS: 4.01 min (96.3%, MH^+ = 274); TLC (ethyl acetate/heptane 1:4): R_f = 0.46; ^1H NMR ($CDCl_3$): δ 3.80 (s, 3H, OCH_3), 5.24 (s, 2H, NCH_2Ar), 6.51 (dd, 1H, J1 = 3.5 Hz,

J2 = 0.8 Hz), 6.57-6.60 (m, 2H), 6.65 (d, 1H, J = 3.1 Hz), 6.66-6.72 (m, 1H), 6.81 (dd, 1H, J1 = 8.6 Hz, J2 = 3.1 Hz), 7.01 (d, 1H, J = 3.5 Hz), 7.53 (d, 1H, J = 8.6 Hz).

(b) 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (Compound 63 . Structure 3 of Scheme I, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)

To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indole (900 mg, 3.29 mmol) in diethyl ether (20 mL) was added dropwise at room temperature a suspension of 2-nitrobenzenesulfenyl chloride (627 mg, 3.31 mmol) in diethyl ether (10 mL) over a period of 2 min. After stirring at room temperature for 1 h ethyl acetate (50 mL) was added and the mixture was washed with saturated $NaHCO_3$ solution (2x50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give an orange-red oil (1.54 g). The crude product was crystallised from toluene/acetone to give the title compound as orange-red crystalline solid (900 mg, yield = 64%).

LCMS: 4.25 min (100%, MH^+ = 427); HPLC: 4.86 min (98.7%); ^1H NMR ($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 5.32 (s, 2H, NCH_2Ar), 6.63-6.69 (m, 2H), 6.72-6.79 (m, 1H), 6.75 (d, 1H, J = 2.7 Hz), 6.85 (dd, 1H, J1 = 8.2 Hz, J2 = 2.7 Hz), 6.98 (dd, 1H, J1 = 6.7 Hz, J2 = 1.2 Hz), 7.16-7.20 (m, 1H), 7.26-7.30 (m, 1H) 7.34 (s, 1H), 7.39 (d, 1H, J = 8.2 Hz), 8.27 (dd, 1H, J1 = 8.2 Hz, J2 = 1.6 Hz).

According to General method 1 the following compounds were prepared:

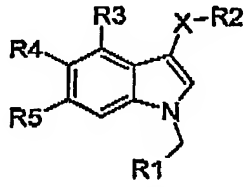


Table 1 Compounds synthesised according to General Method 1

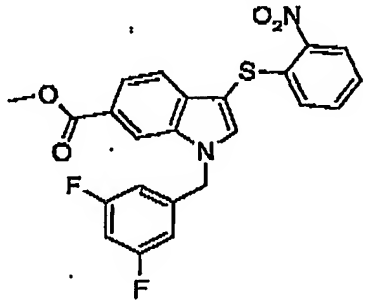
Compound number	X	R^1	R^2	R^3	R^4	R^6	MWt	LCMS (MH+)	LCMS ret. Time[a] (min)
21	S	3,5-difluorophenyl	2-methoxyphenyl	H	H	OMe	411.47	446[c]	5.14[b]
22	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Br	475.32	476	4.89
23	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CF3	464.41	465	5.34[b]
24	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CH2OH	426.44	Nd	3.88[b]

Compound number	X	R^1	R^2	R^3	R^4	R^5	MWt	LCMS (MH+)	LCMS ret. Time[a] (min)
25	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Cl	430.86	431	4.89
50	S	3,5-difluorophenyl	2-nitrophenyl	H	H	F	414.40	415	4.79
51	S	3,5-difluorophenyl	2-nitrophenyl	F	H	H	414.40	415	4.72
52	S	3,5-difluorophenyl	2-nitrophenyl	H	H	H	396.41	397	4.22
53	S	3,5-difluorophenyl	2-nitrophenyl	H	F	H	414.40	415	4.75
54	S	3,5-difluorophenyl	2-nitrophenyl	Cl	H	H	430.86	431	5.14[b]
55	S	3,5-difluorophenyl	2-nitrophenyl	Me	H	H	410.44	411	5.24[b]
56	S	3,5-difluorophenyl	2-nitrophenyl	H	OH	H	412.41	413	4.50[b]
60	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NO2	441.41	442	4.7
61	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OH	412.41	413	4.54[b]
63	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	426.45	274[d]	4.01
66	S	3,5-difluorophenyl	2-pyridyl-N-oxide	H	H	OMe	398.43	399	3.96
90	S	phenyl	2-nitrophenyl	H	H	H	360.43	361	4.19
91	S	phenyl	2-nitrophenyl	H	OMe	H	390.46	391	4.14
92	S	phenyl	2-nitrophenyl	H	H	OMe	390.46	391	4.12

a) 7 min LCMS method was used, unless stated otherwise. b) 10 min LCMS method was used. c) M+Cl. nd = not detected. d) =[M-S($PhNO_2$)]H^+.

Example 2

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methyl ester (Compound 31 , Structure 3 of Scheme I, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=CO_2Me)



(a) 1*H*-Indole-6-carboxylic acid methyl ester (Structure 1 of Scheme I, where R^3=R^4=H, R^5=CO_2Me)

To a solution of 1*H*-Indole-6-carboxylic acid (1.500 g, 9.31 mmol) in methanol (50 mL) was added concentrated H_2SO_4 (550 µL, 10.24 mmol). The mixture was stirred overnight at reflux temperature. The mixture was then neutralised to pH 7 by addition of saturated aqueous $NaHCO_3$ and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow powder. The product was recrystallised from heptane/ethyl acetate to give the title compound as green/yellow crystals (688 mg, yield = 53%)

^{1}H NMR ($CDCl_3$): δ 3.94 (s, 3H, CH_3OCO), 6.60 (m, 1H), 7.37 (t, 1H, J = 4.7 Hz), 7.66 (d, 1H, J = 8.2 Hz), 7.82 (dd, 1H, J1 = 8.2 Hz, J2 = 1.0 Hz), 8.18 (s, 1H), 8.73 (s, 1H, NH)

(b) 1-(3,5-Difluoro-benzyl)-1*H*-indole-6-carboxylic acid methyl ester (Structure 2 of Scheme I, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=CO_2Me)

Under a nitrogen atmosphere: to a solution of 1*H*-indole-6-carboxylic acid methyl ester (367 mg, 2.09 mmol) in DMF (10 mL) was added NaH (60% in oil, 101 mg, 2.52 mmol) at room temperature. After stirring for 15 min 1-bromomethyl-3,5-difluoro-benzene (325 µL, 2.51 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with 3% aqueous citric acid (10 mL) and ethyl acetate (30 mL) was added. The mixture was washed with 3% aqueous citric acid (3x20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (702 mg). The crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:9) to give the title compound as a colourless oil, which slowly crystallised on standing (530 mg, yield = 84%).

LCMS: 4.08 min (99%, MH^+ = 302); ^{1}H NMR ($CDCl_3$): δ 3.92 (3, 3H; CO_2CH_3), 5.37 (s, 2H, NCH_2Ar), 6.54-6.60 (m, 2H), 6.64 (d, 1H, J = 3.1 Hz), 6.67-6.74 (m, 1H), 7.27 (d, 1H, J = 3.1 Hz), 7.68 (d, 1H, J = 8.6 Hz), 7.83 (d, 1H, J = 8.6 Hz), 8.01 (s, 1H).

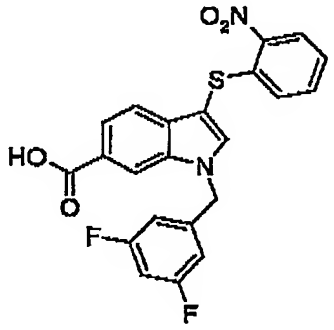
(c) 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methyl ester (Compound 31 , Structure 3 of Scheme I, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=CO_2Me)

To a solution of 1-(3,5-Difluoro-benzyl)-1*H*-indole-6-carboxylic acid methyl ester (330 mg, 1.10 mmol) in dichloromethane (30 mL) was added at room temperature a solution of 2-nitrobenzenesulfenyl chloride (210 mg, 1.11 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 4 days. The reaction mixture was concentrated and the crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:5 to 1:2) to give the title compound as a yellow solid (392 mg, yield = 78%).

HPLC: 4.60 min (97.8%); ^{1}H NMR ($CDCl_3$): δ 3.93 (s, 3H, CO_2CH_3), 5.45 (s, 2H, NCH_2Ar), 6.63-6.69 (m, 2H), 6.74-6.80 (m, 1H), 6.88 (dd, 1H, J1 = 8.2 Hz, J2 = 1.2 Hz), 7.18-7.23 (m, 1H), 7.26-7.30 (m, 1H), 7.57 (d, 1H, J = 7.8 Hz), 7.58 (s, 1H), 7.89 (dd, 1H, J1 = 7.8 Hz, J2 = 1.2 Hz), 8.12 (s, 1H), 8.28 (dd, 1H, J1 = 7.8Hz, J2 = 1.2 Hz).

Example 3

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid (Compound **30**, Structure **14** of Scheme **IV**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H)

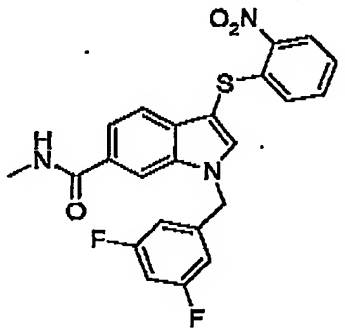


To a solution of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methyl ester (150.0 mg, 0.33 mmol) in dioxane (20 mL) and water (15 mL) was added $LiOH.H_2O$ (83.1 mg, 2.0 mmol) in 5 ml water. The reaction mixture was stirred overnight at 60°C. The mixture was then acidified to pH 4 by addition of 15% aqueous HCl and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow powder. The product was recrystallised from heptane/ethyl acetate to give the title compound as yellow/orange crystals (129.3 mg, y = 89%)

^{1}H NMR (DMSO): δ 5.62 (s, 2H, CH_2Ar), 6.85 (dd, 1H, J1 = 8.6 Hz, J2 = br), 7.05 (m, 2H, br), 7.20 (m, 1H, br), 7.32-7.38 (m, 1H), 7.40 (d, 1H, J = 8.2 Hz), 7.44-7.50 (m, 1H), 7.68 (dd, 1H, J1 = 8.6 Hz, J2 = br), 7.97 (s, 1H, COOH), 8.20 (s, 1H), 8.26 (s, 1H), 8.28 (d, 1H, J = 8.2)

Example 4

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methylamide (Compound 47 , Structure 15 of Scheme IV, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=R^8=H, R^9=Me)



General method 2: amidation of 6-carboxyl indoles of structure **14** to give 6-carboxamideindoles of structure **15** (Scheme IV).

Under nitrogen atmosphere: to a solution of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid (25.1 mg, 57.0 µmol) in dry DMF (10mL) was added NMM (1 mL), HOBt (9.60 mg, 62.7 µmol), EDCI (12.1 mg, 62.7 µmol), and methylammonium chloride (19.2 mg, 285 µmol). The reaction mixture was stirred overnight at room temperature and then poured into ice water. The resulting precipitate was filtered and the residue was washed with excess water followed by little heptane. The product was dried *in vacuo* at 40°C to give the title compound as a yellow solid (15.2 mg, y = 60%).

LCMS: 4.31 min (100.0%, MH^+ = 454); ^{1}H NMR (DMSO): δ 2.80(d, 3H, J = 4.3, CH_3NHCO), 5.63 (s, 2H, CH_2Ar), 6.86 (dd, 1H, J1 = 8.2 Hz, J2 = 1.0 Hz), 7.04 (m, 2H), 7.20 (m, 1H), 7.33-7.37 (m, 1H), 7.41 (d, 1H, 8.6 Hz), 7.46-7.50 (m, 1H), 7.64 (dd, 1H, J1 = 8.2 Hz, J2 = 1.0 Hz), 8.15 (s, 1H), 8.25 (s, 1H), 8.27 (dd, 1H, J1 = 8.6 Hz, J2 = 1.0 Hz), 8.40 (m, 1H, MeNHCO).

According to General method 2 the following compounds were prepared:

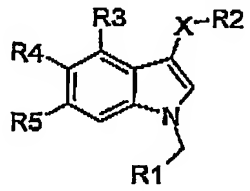


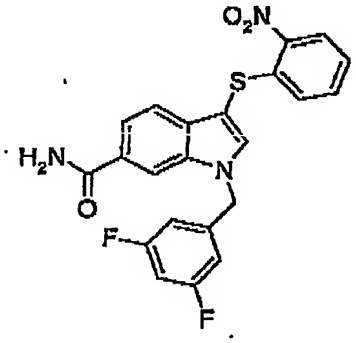
Table 2 Compounds synthesised according to General Method 2

Compound number	X	R^1	R^2	R^3	R^4	R^5	MWt	LCMS (MH+)	LCMS ret. Time[a] (min)
27	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(1-pyrrolidinyl)	493.53	494	4.66
28	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(4-morpholinyl)	509.53	510	4.50
29	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO[1-(4-methylpiperazinyl)]	522.57	523	3.81
32	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONEt2	495.55	496	4.82
34	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2(2-furanyl)	519.53	520	4.74
35	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2(3-pyridyl)	530.55	531	3.94
36	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2NMe2	510.56	511	3.90
37	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2OH	483.49	484	4.21
38	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2OMe	497.52	498	4.48
39	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CO2Me	511.50	512	4.51
40	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CONMe2	524.55	525	4.33
41	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2cPr	493.53	494	4.75
42	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2iPr	495.55	496	4.85
43	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2Ph	529.56	530	4.90
44	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHcPr	479.50	480	4.57
45	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHEt	467.49	468	4.56
46	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHiPr	481.52	482	4.71
47	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHMe	453.47	454	4.31
48	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHnPr	481.52	482	4.75
49	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONMe2	467.49	468	4.30[b]

a) 7 min LCMS method was used, unless stated otherwise. b) 10 min LCMS method was used.

Example 5

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid amide (Compound 33 , Structure 16 of Scheme IV, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H)

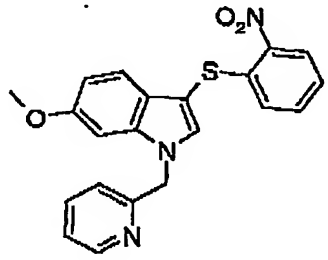


The title compound was prepared according to General method 2, using 51.1 mg (116 µmol) carboxylic acid, 19.5 mg (128 µmol) HOBt, 24.6 mg (128 µmol) EDCI and 31.1 mg (581 µmol) ammonium chloride. The title compound was obtained as a yellow solid (9,0 mg; 18%).

LCMS: 4.16 min (100.0%, MH^+ = 440); ^{1}H NMR ($CDCl_3$): δ 5.46 (s, 2H, CH_2Ar), 6.65 (m, 2H), 6.77 (m, 1H), 6.88 (dd, 1H, J1 = 8.2 Hz, J2 = 1.0 Hz)), 7.21 (m, 1H), 7,29 (m, 1H), 7.51 (dd, 1H, J1 = 7.8 Hz, J2 = 1.0 Hz), 7.57 (d, 1H, J = 7.7 Hz), 7.58 (s, 1H), 8.05 (s, 1H), 8.29 (dd, 1H, J1 = 8.2 Hz, J2 = 1.0 Hz).

Example 6

6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole (Compound 9 , Structure 3 of Scheme I, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)



General method 3: 3-sulfenylation of a (un)substituted indole of structure **1** to give substituted indoles of structure **4**, followed by indole-*N*-alkylation to give N-alkylated indole structure **3** (Scheme I).

(a) <u>6-Methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (Structure 4 of Scheme I, where R^2 = 2-nitrophenyl, R^1=R^3=R^4=H, R^5=OMe)</u>

To a solution of 6-methoxyindole (1.5 g, 10.2 mmol) in Et_2O (100 mL) was added a solution of 2-nitrobenzenesulfenylchloride (1.93 g, 10.2 mmol) in 50 mL Et_2O dropwise, over a 4 minute period. The resulting yellow solution was stirred at room temperature for 1 h. The solvent was evaporated and the crude product was purified over a silica column (heptane/ethyl acetate 9:1) to give the title compound (3.054 g, yield = 97%).

HPLC : 3.72 min. purity 96.7%, TLC (heptane/ethyl acetate 1:1): R_f = 0.6;

^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3H, OCH3), 6,84 (dd, 1H, J1 = 7.8 Hz, J2 = 3,13 Hz), 6.97 (m, 2H), 7.16 (t, 1H, J = 7.8Hz), 7.25 (t, 1H, J = 7.8Hz), 7.36 (d, 1H, J = 7.8 Hz), 7.44 (d, 1H, J = 2.0 Hz), 8.26 (d, 1H, J = 7.8 Hz), 8.45 (s, 1H, NH).

(b) <u>6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole (Compound 9 , Structure 3 of Scheme I, where R^1 = 2-pyridyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)</u>

To a solution of 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (1.5 g, 5 mmol) in DMF (150 mL) was added NaH (60% in oil; 500 mg, 12.5 mmol) in small portions, over a 4 minute period. The resulting dark solution was stirred for 5 min. at room temperature. Then 2-picolyl chloride hydrochloride (984 mg, 6 mmol) was added in small portions, over a 2 minute period. During stirring at room temperature (2h) the colour of the solution slightly changed from dark to yellow. Ethyl acetate (100 mL) was added and the mixture was washed with 2% aqueous citric acid (2x100 mL) and water (100 mL). The organic phase was dried (MgSO4) and the solvent was evaporated. The crude product was purified by crystallisation (ethyl acetate/heptane) to give the title compound (1.437 g, yield = 74%).

HPLC : 10.3 min, purity 99.6%, TLC (heptane/ethyl acetate 1:1): R_f = 0.3;

^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3H, OCH3), 5.47 (s, 2H, NCH_2), 6.82 (m, 2H), 6.88 (d, 1H, J = 7.8 Hz), 7.01 (dd, 1H, J1 = 7.8 Hz, J2 = 1,6 Hz), 7.15-7.19 (m, 1H), 7.25 (m,

2H), 7.37 (d, 1H, j = 8.6 Hz), 7.60-7.64 (m, 1H), 8.26 (dd, 1H, J1 = 7.8 Hz, J2 = 1.6 Hz), 8.63 (d, 1H, J = 5.88 Hz).

According to General method 3 the following compounds were prepared:

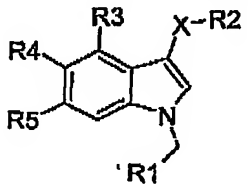


Table 3 Compounds synthesised according to General Method 3

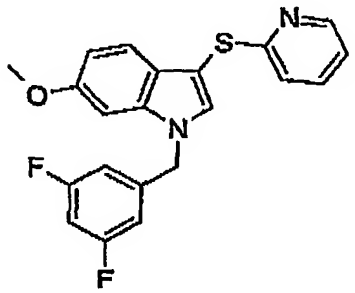
Compound number	X	R^1	R^2	R^3	R^4	R^5	MWt	LCMS (MH+)	LCMS ret. Time[a] (min)
1	S	2,5-difluorophenyl	2-nitrophenyl	H	H	OMe	426.44	427	4.07
2	S	2,fluoro,3-methylphenyl	2-nitrophenyl	H	H	OMe	422.48	423	4.23
3	S	2-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	425	4.17
4	S	2-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	416	3.97
5	S	2-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	409	4.10
6	S	2-methyl,3-nitrophenyl	2-nitrophenyl	H	H	OMe	449.48	450	4.10
7	S	2-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	405	4.16
8	S	2-nitrophenyl	2-nitrophenyl	H	H	OMe	435.46	436	4.08
9	S	2-pyridyl	2-nitrophenyl	H	H	OMe	391.45		10.30[b]
11	S	2-tetrahydropyranyl	2-nitrophenyl	H	H	OMe	398.48	399	4.68
12	S	2-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	458.46	459	4.29
13	S	3-(5-methylisoxazolyl)	2-nitrophenyl	H	H	OMe	395.44	396	4.66
14	S	3,4-dichlorophenyl	2-nitrophenyl	H	H	OMe	459.35	459	4.33
15	S	3,5-dichlorophenyl	2-nitrophenyl	H	H	OMe	459.35	459	4.36
67	S	3-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	425	4.34
68	S	3-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	416	3.92
69	S	3-fluoro,5-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	476.45	477	4.42
70	S	3-fluoro,6-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	476.45	477	4.27
71	S	3-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	409	4.22
72	S	3-methoxyphenyl	2-nitrophenyl	H	H	OMe	420.49	421	4.04
73	S	3-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	405	4.16
74	S	3-nitrophenyl	2-nitrophenyl	H	H	OMe	435.46	436	4.00

Compound number	X	R^1	R^2	R^3	R^4	R^5	MWt	LCMS (MH+)	LCMS ret. Time[a] (min)
75	S	3-pyridyl	2-nitrophenyl	H	H	OMe	391.45	392	3.28
76	S	3-trifluoromethyl,4-chlorophenyl	2-nitrophenyl	H	H	OMe	492.90	493	4.33
77	S	3-trifluoromethyloxyphenyl	2-nitrophenyl	H	H	OMe	474.46	475	4.43
78	S	3-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	458.46	459	4.21
79	S	4-(2-methylthiazolyl)	2-nitrophenyl	H	H	OMe	411.50	412	4.39
80	S	4-(3,5-dimethylisoxazolyl)	2-nitrophenyl	H	H	OMe	409.46	410	4.49
81	S	4-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	425	4.22
82	S	4-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	416	3.93
83	S	4-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	409	4.07
84	S	4-methoxyphenyl	2-nitrophenyl	H	H	OMe	420.49	421	4.03
85	S	4-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	405	4.19
86	S	4-morpholinyl	2-nitrophenyl	H	H	OMe	413.50	414	3.54
87	S	5-(2-chlorothiazolyl)	2-nitrophenyl	H	H	OMe	431.92	432	4.61
88	S	5-(2-chlorothiophenyl)	2-nitrophenyl	H	H	OMe	430.93	431	4.92
89	S	cyclohexyl	2-nitrophenyl	H	H	OMe	396.51	397	5.11

a) 7 min LCMS method was used unless stated otherwise. b) a 20 min run on an HPLC system was used.

Example 7

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(pyridin-2-ylsulfanyl)-1*H*-indole (Compound 65, Structure 3 of Scheme I, where R^1 = 3,5-difluorophenyl, R^2 = 2-pyridyl, R^3=R^4=H, R^5=OMe)



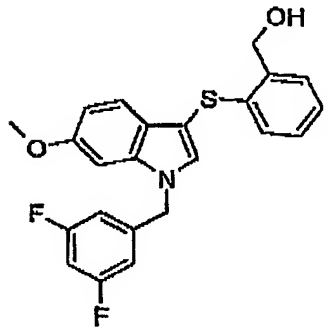
Under a nitrogen atmosphere: to a cooled (-10°C) solution of 2-mercaptopyridine (25 mg, 0.22 mmol) in CCl_4 (2 mL) was passed Cl_2-gas during a period of 1 minute. The solvent was evaporated and a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indole (25 mg, 0.09 mmol) in Et_2O (2 mL) was added dropwise. The reaction mixture was concentrated and the crude product was purified by preparative LCMS to give the title compound (7.77 mg, yield = 23%).

LCMS : 3.95 min (100%, MH^+ 383); TLC (heptane/ethyl acetate 1:1): R_f= 0.6;

^{1}H-NMR ($CDCl_3$) : δ 2.23 (s, 1H, NH), 3.82 (s, 1H, OCH_3), 6.65 (m, 2H), 6.73 (d, 1H, J = 2.7 Hz), 6.73-6.78 (m, 1H), 6.80 (d, 1H, J = 7.8 Hz), 6.87 (dd, 1H, J1 = 7.8 Hz, J2 = 1.6 Hz), 7.00 (ddd, 1H, J1 = 9.8 Hz, J2 = 4.7 Hz, J3 = 0.8 Hz), 7.35 (s, 1H), 7.42 (ddd, 1H, J1 = J2 = 7.8 Hz, J3 = 1.6 Hz), 7.50 (d, 1H, 8.6 Hz), 8.46 (d, 1H, J = 4.7 Hz).

Example 8

{2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-phenyl}-methanol (Compound 16 , Structure 8 of Scheme III, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)



a) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (Compound 19 , Structure 7 of Scheme III, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

Chlorine gas was bubbled through CCl_4 (5 mL) at -10°C for 3 min. Then a solution of methylthiosalicylate (91 µL, 0.66 mmol) in CCl_4 (2 mL) was added. The mixture was stirred at -10°C for 5 min and then at room temperature for 15 min. The mixture was concentrated and redissolved in CH_2Cl_2 (5 mL). To this solution a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indole (121 mg, 0.443 mmol) in CH_2Cl_2 (3 mL) was

added dropwise. The mixture was stirred at room temperature for 2 h and was concentrated. The crude product was purified by column chromatography (ethyl acetate/heptane 1:9) to give the title compound as a white solid (161 mg, 83% yield). LCMS: 4.72 min (MH^+ = 440); ^{1}H-NMR ($CDCl_3$) : δ 3.82 (s, 3H, $ArOCH_3$), 3.99 (s, 3H, CO_2CH_3), 5.30 (s, 2H, CH_2Ar), 6.62-6.69 (m, 2H), 6.71-6.77 (m, 2H), 6.83 (dd, 1H, J1 = 8.6 Hz, J2 = 2.4 Hz), 6.87 (dd, 1H, J1 = 8.4 Hz, J2 = 1.2 Hz), 7.06-7.11 (m, 1H), 7.15-7.20 (m, 1H), 7.30 (s, 1H), 7.44 (d, 1H, J = 8.6 Hz), 8.02 (dd, 1H, J1 = 8.0 Hz, J2 = 1.2 Hz).

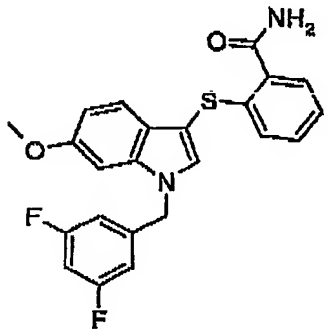
b) {2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-phenyl}-methanol (Compound 16 , Structure 8 of Scheme III, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

Under a nitrogen atmosphere: to a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (13.5 mg, 0.031 mmol) in THF (2 mL) was added $LiAlH_4$ (1.0 M in THF, 0.040 mL, 0.040 mmol). The mixture was stirred at room temperature for 3 h. Then ethyl acetate (25 mL) was added and the mixture was washed with 3% aqueous citric acid (2x25 mL) and brine (25 mL). The organic phase was dried ($MgSO_4$) and concentrated to give a colourless oil (15 mg). The crude product was purified by prep. HPLC to give the title compound as a colourless oil (5.6 mg, 44% yield).

LCMS: 4.47 min (95.6%, MH^+ = 412); ^{1}H-NMR ($CDCl_3$) : δ 3.49 (s, 1H, OH), 3.81 (3, 3H, OCH_3), 4.92 (s, 2H, CH_2OH), 5.28 (s, 2H, CH_2Ar), 6.62-6.66 (m, 2H), 6.70-6.77 (m, 2H), 6.83 (dd, 1H, J1 = 8.8 Hz, J2 = 2.4 Hz), 6.89 (dd, 1H, J1 = 8.0 Hz, J2 = 1.2 Hz), 7.02-7.07 (m, 1H), 7.08-7.13 (m, 1H), 7.29 (s, 1H), 7.38 (dd, 1H, J1 = 8.0 Hz, J2 = 1.2 Hz), 7.44 (d, 1H, J = 8.8 Hz).

Example 9

2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzamide (Compound 18, Structure 11 of Scheme III, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)



a) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid (Structure 9 of Scheme III, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

To a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (97 mg, 0.221 mmol) in THF (10 mL) was added a solution of $LiOH \cdot H_2O$ (71 mg, 1.69 mmol) in water (10 mL). The mixture was stirred at room temperature for 17 h and then at 60°C for 24 h and was then acidified with 3% aqueous citric acid. Ethyl acetate (50 mL) was added and the mixture was washed with 3% aqueous citric acid (2x50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated to give a yellow solid (104 mg). The crude product was recrystallised from ethyl acetate/heptane to give the title compound as a yellow powder (49 mg, 52% yield).

LCMS: 4.37 min (MH^+ = 426); ^{1}H-NMR ($CDCl_3$) : δ 3.77 (s, 3H, OCH_3), 5.51 (s, 2H, CH_2Ar), 6.69 (d, 1H, J = 8.0 Hz), 6.76 (dd, 1H, J1 = 8.4 Hz, J2 = 2.4 Hz), 6.98-7.04 (m, 2H), 7.11-7.15 (m, 1H), 7.16-7.25 (m, 4H), 7.83 (s, 1H), 7.92 (dd, 1H, J1 = 8.0Hz, J2 = 1.6 Hz).

General method 4: Reaction of an amine with a carboxylic acid of structure **9**, with TBTU and DIPEA, to give amides of structure **3**, in which R^2 = phenyl-2-carboxamide, exemplified by compounds of structure **10** and **11** (Scheme **III**).

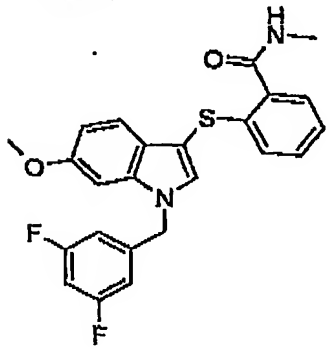
b) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzamide (Compound **18**, Structure **11** of Scheme **III**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

Through a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid (36 mg, 0.085 mmol), TBTU (28 mg, 0.087 mmol) and DIPEA (30 µL, 0.172 mmol) in DMF (1 mL) was bubbled NH_3 gas for 10 min. The mixture was then stirred at room temperature for 3 days. Then 3% aqueous citric acid (0.4 mL) was added and the crude reaction mixture was purified over a RP-SPE cartridge (2g sorbent; 25% aqueous methanol to 100% methanol) to give a white solid (34 mg). The crude product was purified by column chromatography (ethyl acetate) to give the title compound as a colourless oil, which solidifies on standing (31 mg, yield: 86%).

LCMS: 4.20 min (MH^+ = 425); ^{1}H-NMR ($CDCl_3$) : δ 3.81 (s, 3H, OCH_3), 5.39 (s, 2H, CH_2Ar), 6.05 (s, br, 1H, NH), 6.28 (s, br, 1H, NH), 6.61-6.67 (m, 2H), 6.70-6.72 (m, 1H), 6.73-6.77 (m, 1H), 6.83 (dd, 1H, J1 = 8.8 Hz, J2 = 2:0 Hz), 6.92 (dd, 1H, J1 = 8.0 Hz, J2 = 1.2 Hz), 7.07-7.17 (m, 2H), 7.31 (s, 1H), 7.45 (d, 1H, J = 8.8 Hz), 7.60 (dd, 1H, J1 = 8.0 Hz, J2 = 1.2 Hz).

Example 10

2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-*N*-methyl-benzamide (Compound **17**, Structure **10** of Scheme **III**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

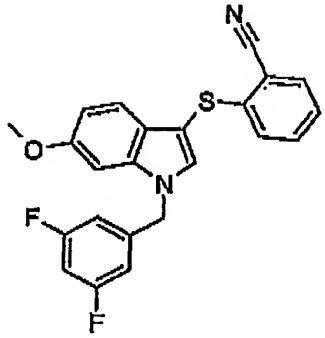


According to general method 4 compound **17** was synthesised from methylamine.

LCMS: 4.07 min (MH^+ = 439).

Example 11

2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzonitrile (Compound **20**, Structure **12'** of Scheme **III**, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, R^5=OMe)

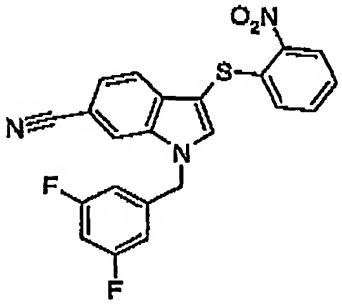


To a cooled (0°C) solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzamide (8 mg, 0.019 mmol) and Et_3N (10 µL, 0.072 mmol) in CH_2Cl_2 (1.5 mL) was added Tf_2O (6 µL, 0.036 mmol). The mixture was stirred at 0°C for 2 h and then at room temperature for 22 h. Water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (2x25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a brown oil (25 mg). The crude product was purified by column chromatography (ethyl acetate/heptane 1:2) to give the title compound as a pale pink oil (3 mg, yield: 39%).

LCMS: 4.57 min ($MH^+ = 407$); ^{1}H-NMR ($CDCl_3$): δ 3.82 (s, 3H. OCH_3), 5.30 (s, 2H, CH_2Ar), 6.62-6.67 (m, 2H), 6.71-6.73 (m, 1H), 6.74-6.78 (m, 1H), 6.86 (dd, 1H, J1 = 8.8 Hz, J2 = 2.0 Hz), 6.91 (d, 1H, J = 8.4 Hz), 7.11-7.15 (m, 1H), 7.26-7.30 (m, 1H), 7.37 (s, 1H), 7.46 (d, 1H, J = 8.8 Hz), 7.57-7.60 (m, 1H).

Example 12

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carbonitrile (Compound 26, Structure 17 of Scheme IV, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H)

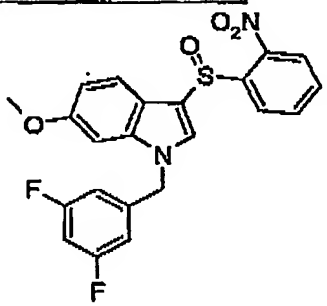


To a cooled (0°C) suspension of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid amide (15 mg, 0.034 mmol) and Et_3N (10 µL, 0.072 mmol) in CH_2Cl_2 (1.5 mL) was added Tf_2O (13 µL, 0.077 mmol). The mixture was stirred at 0°C for 2 h and then at room temperature for 20 h. Water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (2x25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give the title compound as a yellow solid (13 mg, yield: 91%).

LCMS: 4.55 min (MH^+ = not detectable); ^{1}H-NMR ($CDCl_3$): δ 5.42 (s, 2H, CH_2Ar), 6.63-6.69 (m, 2H), 6.78-6.85 (m, 2H), 7.21-7.25 (m, 1H), 7.28-7.33 (m, 1H), 7.44 (dd, 1H, J1 = 8.4 Hz, J2 = 1.2 Hz), 7.62 (d, 1H, J = 8.4 Hz), 7.66 (s, 1H), 8.29 (dd, 1H, J1 = 8.4 Hz, J2 = 1.6 Hz).

Example 13

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-benzenesulfinyl)-1*H*-indole (Compound 64, Structure 5 of Scheme II, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)

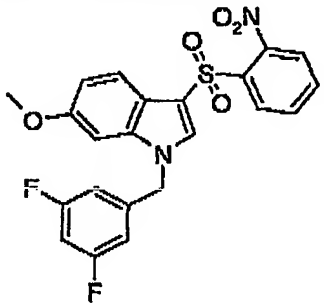


To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (40 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) was added meta-chloroperbenzoic acid (14.5, 0.08 mmol). The solution was stirred at room temperature for 2 h. The solvent was evaporated and the crude product was purified by prep LC-MS to give the title compound (14.3 mg, yield = 34%).

HPLC : 4.13 min, purity 100%; TLC (heptane/ethyl acetate 1:1) : Rf = 0.4; ^{1}H NMR ($CDCl_3$): δ 3.66 (s, 3H, OCH3), 5.12 (s, 2H), 6.57 (m, 3H), 6.75 (m, 2H), 7.47 (d, 1H, J = 7.8 Hz), 7.52 (s, 1H), 7.66-7.70 (m, 1H), 8.28-8.32 (m, 1H), 8.23 (dd, 1H, J1 = 7.8 Hz, J2 = 1.9 Hz), 8.80 (dd, 1H, J1 = 7.8 Hz, J2 = 3.1 Hz).

Example 14

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-benzenesulfonyl)-1*H*-indole (Compound 62, Structure 6 of Scheme II, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, R^5=OMe)

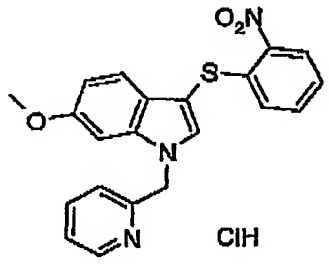


To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (40 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) was added meta-chloroperbenzoic acid (46.5 mg, 0.27 mmol). The solution was stirred at room temperature for 6 h. The solvent was evaporated and the crude product was purified by LC-MS to give the title compound (14.5 mg, yield = 34%).

HPLC: 4.38 min. purity 100%; TLC (heptane/ethyl acetate 1:1) : Rf = 0.6; ^{1}H NMR ($CDCl_3$): δ 3.71 (s, 3H, OCH3), 5.25 (s, 2H), 6.58 (d, 1H, J = 3.1), 6.62 (m, 1H), 6.07-6.11 (m, 1H), 6.88 (dd, 1H, J1 = 7.8 Hz, J2 = 3.1 Hz), 7.63 (m, 4H), 7.72 (d, 1H, J = 7.8 Hz), 7.83 (s, 1H), 8.37 (dd, 1H, J1 = 7.8 Hz, J2 = 1.9 Hz).

Example 15

2-[6-Methoxy-3-(2-nitro-phenylsulfanyl)-indol-1-ylmethyl]-pyridinium chloride (Compound 10)

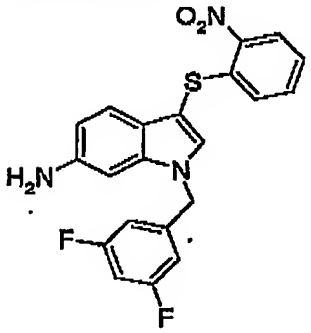


To a solution of 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole in methylene chloride was passed HCl-gas till the organic salt crystallised. The title compound was isolated by filtration.

LC-MS : 4.04 min (MH^+ = 392); ^{1}H NMR (DMSO): δ 3.78 (s, 3H, OCH3), 5.78 (s, 2H, NCH_2), 6.77 (dd, 1H, J1 = 7.8 Hz, J2 = 2.0 Hz), 6.93 (dd, 1H, J1 = 7.8 Hz, J2 = 0.8 Hz), 7.22 (d, 1H, J = 7.8 Hz), 7.26 (d, 1H, J = 2.0 Hz), 7.34 (m, 2H), 7.48-7.52 (m, 1H), 7.59 (t, 1H, J = 7.0 Hz), 7.96 (s, 1H), 8.08 (t, 1H, J = 7.0 Hz), 8.27 (dd, 1H, J1 = 7.8 Hz, J2 = 1.6 Hz), 8.74 (d, 1H, J = 6.7 Hz).

Example 16

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine (Compound 57, Structure 23 of Scheme V, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H)



a) 1-(3,5-Difluoro-benzyl)-6-nitro-1*H*-indole (Structure 19 of Scheme V, where R^1 = 3,5-difluorophenyl, R^3=R^4=H)

To a solution of 6-nitroindole (162 mg, 1.0 mmol) in DMF (4 mL) was added NaH (60% dispersion on oil; 80 mg, 2.0 mmol). The resulting dark solution was stirred at room temperature for 15 minutes. 3,5-difluorobenzyl bromide (129 µL, 1,1 mmol) was added. The reaction mixture was stirred overnight, poured into acidified water and extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*.

The product was purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as a yellow solid (270 mg, yield = 94%).

LCMS: 5.54 min (100.0%, MH^+ = 289); ^{1}H NMR ($CDCl_3$): δ 5.40 (s, 2H, CH_2Ar), 6.58 (m, 2H), 6.71 (d, 1H, J = 3.5 Hz), 6.75 (m, 1H), 7.26 (s, 1H), 7,41 (d, 1H, J = 3.5 Hz), 7.71 (d, 1H, J = 8.3 Hz), 8.05 (dd, 1H, J1 = 8.3 Hz, J2 = 2.0 Hz), 8.21 (d, 1H, J = 2.0 Hz).

b) 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (Structure **20** of Scheme **V**, where R^1 = 3,5-difluorophenyl. R^3=R^4=H)

To a solution of 1-(3,5-Difluoro-benzyl)-6-nitro-1*H*-indole (144 mg, 0.5 mmol) in ethanol (20 mL) was added hydrochloric acid 37% (80 µL) and $SnCl_2.2H_2O$ (600 mg). The reaction mixture was stirred at 60 °C for 40 h and was then concentrated *in vacuo*. The residue was poured into ethyl acetate and a concentrated $NaHCO_3$-solution was added. The two-layer phase system was filtered over decalite to get rid of the tin salts and the filtrate was twice extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as a colourless oil (89 mg, yield = 69%).

LCMS: 3.20 min (97.7%, MH^+ = 259); ^{1}H NMR ($CDCl_3$): δ 5.12 (s, 2H, CH_2Ar), 6.52 (m, 2H), 6.56 (d, 1H, J = 3.5 Hz), 6.63 (m, 1H), 7.97 (dd, 1H, J1 = 8.3 Hz, J2 = 2.0 Hz), 7.13 (d, 1H, J = 3.5 Hz), 7,17 (d, 1H, J = 2.0 Hz), 7.55 (d, 1H, J = 8.3 Hz).

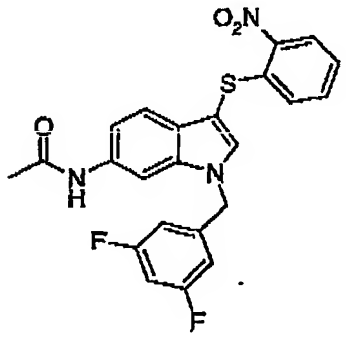
c) 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine (Compound 57, Structure **23** of Scheme **V**, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H)

To a solution of 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (25 mg, 0.1 mmol) in DCM (4 mL) was added 2-nitrobenzenesulfenyl chloride. The resulting yellow solution was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as an orange solid (11.6 mg, yield = 28%).

LCMS: 5.11 min (100.0%, MH^+ = 412); ^{1}H NMR ($CDCl_3$): δ 5.22 (s, 2H, CH_2Ar), 6.56 (m, 2H), 6.65 (m, 1H), 6.84 (dd, 1H, J1 = 8.2 Hz, J2 = 1.2 Hz), 7.00 (dd, 1H, J1 = 8.2 Hz, J2 = 1.2 Hz), 7.19 (m, 1H), 7.30 (d, 1H, J = 1.2 Hz), 7.31 (s, 1H), 7.37 (d, 1H, J = 8.2 Hz) 7.49 (m, 1H), 8.27 (dd, 1H, J1 = 8.2 Hz, J2 = 1.2 Hz).

Example 17

N-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-acetamide (Compound 58, Structure 22 of Scheme V, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z = methyl)



General method 5: Reaction of an acid anhydride with a 6-aminoindole of structure **20** to give compounds of structure **21**, followed by sulfanylation of the indole 3-position to give compounds of structure **22** (Scheme V).

a) *N*-[1-(3,5-Difluoro-benzyl) -1*H*-indol-6-yl]-acetamide (Structure 21 of Scheme V, where R^1 = 3,5-difluorophenyl, R^3=R^4=H, Z = methyl)

To a solution of 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (25 mg, 0.1 mmol) in DCM (4 mL) was added pyridine (25 µL) and acetic anhydride (9.8 µL, 0.11 mmol) and stirred overnight at room temperature. The reaction mixture was poured into 10 mL of water and neutralised with $NaHCO_3$ and extracted twice with DCM. De combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude compound as a off white solid (23.3 mg, yield = 84%). The product was used without further purification.

LCMS: 4.10 min (97.4%, MH^+ = 301); ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3H, CH_3CON), 5.28 (s, 2H, CH_2Ar), 6.53 (d, 1H, J = 3.1), 6.58 (m, 2H), 6.68 (m, 1H), 6.87 (dd, 1H, J1 = 8.3 Hz, J2 = 1.6 Hz), 7.07 (d, 1H, J = 3.1 Hz), 7,55 (d, 1H, J = 8.3 Hz), 7.90 (s, 1H).

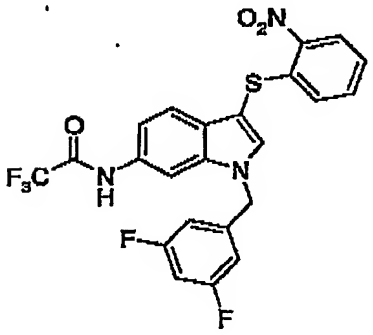
b) *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-acetamide (Compound 58, Structure 22 of Scheme V, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z = methyl)

To a solution of *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-acetamide (23.3 mg, 0.08 mmol) in diethyl ether (4 mL) was added 2-nitrobenzenesulfenyl chloride (14.7 mg,

0.09 mmol). The resulting yellow solution was stirred overnight at room temperature. The mixture was concentrated *in vacuo* and purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as a yellow solid (35.0 mg, yield = 96%).
LCMS: 4.26 min (98.6%, $MH^+ = 454$); ^1H NMR (DMSO): δ 2.03 (s, 3H, CH_3CON), 5.51 (s, 2H, CH_2Ar), 6.89 (dd, 1H, J = 8.3 Hz, J2 = 1.2 Hz), 6.95 (m, 2H), 7.17 (dd, 1H, J1 = 8.3 Hz, J2 = 2.0 Hz), 7.19 (m, 1H), 7.27 (d, 1H, J = 8.3 Hz), 7,34 (m, 1H), 7.49 (m, 1H), 7.97 (d, 1H, J = 1.2 Hz), 8.02 (s, 1H), 8.27 (dd, 1H, J1 = 8.3 Hz, J2 = 1.2 Hz).

Example 18

N-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide (Compound 59, Structure 22 of Scheme V, where R^1 = 3,5-difluorophenyl, R^2 = 2-nitrophenyl, R^3=R^4=H, Z = trifluoromethyl)



According to General method 5, step a): *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide was prepared using 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (17.7 mg, 69 µmol), pyridine (17 µL) and trifluoroacetic anhydride (9,68 µL, 70 µmol). The compound was purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as a white solid (10.9 mg, yield = 61%).
LCMS: 4.41 min (82.1%, $MH^+ = 355$)
According to General method 5, step b): *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide was prepared using *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide (10.9 mg, 31 µmol) and 2-nitrobenzenesulfenylchloride (5.7 mg, 37 µmol). The compound was purified over an HPLC column ($MeCN/H_2O$) to give the title compound as a yellow solid (10.2 mg, yield = 65%).
LCMS: 4.65 min (89.0%, $MH^+ = 508$); ^1H NMR (DMSO): δ 5.56 (s, 2H, CH_2Ar), 6.87 (dd, 1H, J = 8.3 Hz, J2 = 1.2 Hz), 7.01 (m, 2H), 7.20 (m, 1H), 7.35 (m, 1H), 7.37 (dd,

1H, J1 = 8.3 Hz, J2 = 2.0 Hz), 7.39 (d, 1H, J = 8.3 Hz), 7.49 (m, 1H), 7,50 (d, 1H, J = 2.0 Hz), 8.15 (s, 1H), 8.28 (dd, 1H, J1 = 8.3 Hz, J2 = 2.0 Hz).

Compounds were tested for their Androgen Receptor activity in a transactivation assay and in a binding assay.

The (anti-)androgenic activity of test compounds (EC50 and intrinsic activity) was determined in an *in vitro* bioassay of Chinese hamster ovary (CHO) cells stably transfected with the human androgen receptor expression plasmid and a reporter plasmid in which the MMTV-promoter is linked to the luciferase reporter gene. The cell-line CHO-AR-pMMTV-LUC 1G12-A5-CA is described in Schoonen et al. (2000), Journal of Steroid Biochemistry and Molecular Biology 74(4):213-222. The antiandrogenic activity of a test compound was determined by the inhibition of the transactivation via the androgen receptor of the enzyme luciferase in the presence of 1 nM DHT (5α-dihydrotestosterone, 17β-hydroxy-5α-androstan-3-one). Intrinsic activity of antiandrogenic activity was determined in the presence of the reference antiandrogen 2-Hydroxy-2-methyl-*N*-(4-nitro-3-trifluoromethyl-phenyl)-propionamide (Hydroxyflutamide), and set at 100%. For androgenic activity, maximal intrinsic activity in the presence of 100 nM DHT was set at 100%.

Determination of competitive binding to cytoplasmic human androgen receptor from recombinant CHO cells is used to estimate the relative binding affinity (RBA) of a test compound for androgen receptors present in the cytosol prepared of the recombinant CHO cell-line, CHO-AR-pMMTV-LUC 1G12-A5-CA. The RBA for the test compound is given relative to DHT.

The results of both determinations are presented in Table 4.

Table 4 Androgen receptor activity

Cpd. number	X	R^1	R^2	R^3	R^4	R^5	ago EC50	ago efficacy	ant EC50	ant efficacy
1	S	2,5-difluorophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
2	S	2,fluoro,3-methylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
3	S	2-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
4	S	2-cyanophenyl	2-nitrophenyl	H	H	OMe	+	±	++	±

Cpd. number	X	R^1	R^2	R^3	R^4	R^5	ago EC50	ago efficacy	ant EC50	ant efficacy
5	S	2-fluorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
6	S	2-methyl,3-nitrophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
7	S	2-methylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
8	S	2-nitrophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
9	S	2-pyridyl	2-nitrophenyl	H	H	OMe	+++	+	+++	±
10	S	2-pyridyl HCl salt	2-nitrophenyl	H	H	OMe	++	+	-	-
11	S	2-tetrahydropyranyl	2-nitrophenyl	H	H	OMe	++	+	-	-
12	S	2-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
13	S	3-(5-methylisoxazolyl)	2-nitrophenyl	H	H	OMe	+	±	-	-
14	S	3,4-dichlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
15	S	3,5-dichlorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
16	S	3,5-difluorophenyl	2-(hydroxymethylphenyl)	H	H	OMe	++	+	++	±
17	S	3,5-difluorophenyl	2-(N-methylbenzamide)	H	H	OMe	-	-	+	+
18	S	3,5-difluorophenyl	2-benzamide	H	H	OMe	++	+	++	±
19	S	3,5-difluorophenyl	2-benzoic acid methyl ester	H	H	OMe	+	+	-	-
20	S	3,5-difluorophenyl	2-cyanophenyl	H	H	OMe	++	++	-	-
21	S	3,5-difluorophenyl	2-methoxyphenyl	H	H	OMe	++			
22	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Br	++	++	-	-
23	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CF3	+++	++	-	-
24	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CH2OH	++	++	-	-
25	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Cl	+++	++	-	-
26	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CN	+++	++	-	-
27	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(1-pyrrolidinyl)	++	+	-	-
28	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(4-morpholinyl)	++	+	-	-
29	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO[1-(4-methylpiperazinyl)]	++	++	-	-
30	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO2H	+	+	-	-
31	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO2Me	+++	+	-	-
32	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONEt2	++	+	+	±
33	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONH2	+++	++	-	-
34	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2(2-furanyl)	++	+	-	-
35	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2(3-pyridyl)	++	±	-	-
36	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2Nmc2	++	+	-	-

Cpd. number	X	R^1	R^2	R^3	R^4	R^5	ago EC50	ago efficacy	ant EC50	ant efficacy
37	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2OH	+++	++	-	-
38	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CH2OMe	+++	++	-	-
39	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CO2Me	++	++	-	-
40	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CONMe2	++	+	-	-
41	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2cPr	+++	+	-	-
42	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2iPr	++	+	-	-
43	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2Ph	++	±	+	±
44	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHcPr	+++	+	-	-
45	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHEt	+++	++	-	-
46	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHiPr	++	+	++	±
47	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHMe	+++	+	-	-
48	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHnPr	++	+	+	±
49	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONMe2	+++	+	-	-
50	S	3,5-difluorophenyl	2-nitrophenyl	H	H	F	++	++	-	-
51	S	3,5-difluorophenyl	2-nitrophenyl	F	H	H	+++	++	-	-
52	S	3,5-difluorophenyl	2-nitrophenyl	H	H	H	++	++	-	-
53	S	3,5-difluorophenyl	2-nitrophenyl	H	F	H	++	++	-	-
54	S	3,5-difluorophenyl	2-nitrophenyl	Cl	H	H	++	++	-	-
55	S	3,5-difluorophenyl	2-nitrophenyl	Me	H	H	++	+	-	-
56	S	3,5-difluorophenyl	2-nitrophenyl	H	OH	H	+++			
57	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NH2	+	+	-	-
58	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHAc	+++	++	-	-
59	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOCF3	+++	+	-	-
60	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NO2	+++	++	-	-
61	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OH	+++			
62	SO2	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
63	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
64	SO	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	-	±	+	+
65	S	3,5-difluorophenyl	2-pyridyl	H	H	OMe	++	++	-	-
66	S	3,5-difluorophenyl	2-pyridyl-N-oxide	H	H	OMe	+	+	++	±
67	S	3-chlorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
68	S	3-cyanophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
69	S	3-fluoro,5-	2-nitrophenyl	H	H	OMe	++	++	-	-

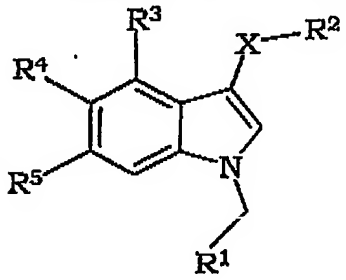
Cpd. number	X	R^1	R^2	R^3	R^4	R^5	ago EC50	ago efficacy	ant EC50	ant efficacy
		trifluoromethylphenyl								
70	S	3-fluoro,6-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
71	S	3-fluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
72	S	3-methoxyphenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
73	S	3-methylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
74	S	3-nitrophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
75	S	3-pyridyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
76	S	3-trifluoromethyl,4-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
77	S	3-trifluoromethyloxyphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
78	S	3-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
79	S	4-(2-methylthiazolyl)	2-nitrophenyl	H	H	OMe	++	+	-	-
80	S	4-(3,5-dimethylisoxazolyl)	2-nitrophenyl	H	H	OMe	+	±	+	±
81	S	4-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	+++	+
82	S	4-cyanophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
83	S	4-fluorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
84	S	4-methoxyphenyl	2-nitrophenyl	H	H	OMe	+	±	±	++
85	S	4-methylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	±
86	S	4-morpholinyl	2-nitrophenyl	H	H	OMe	±	±	+	+
87	S	5-(2-chlorothiazolyl)	2-nitrophenyl	H	H	OMe	++	+	-	-
88	S	5-(2-chlorothiophenyl)	2-nitrophenyl	H	H	OMe	++	++	-	-
89	S	Cyclohexyl	2-nitrophenyl	H	H	OMe	++	+	+++	±
90	S	Phenyl	2-nitrophenyl	H	H	H	+	+	-	-
91	S	Phenyl	2-nitrophenyl	H	OMe	H	-	-	±	++
92	S	Phenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-

note 1: EC50 scale: +++ <5 nM; ++ between 5 and 100 nM; + <1000 nM; ± between 1000 and 10000 nM; - >10000 nM

note 2: efficacy scale (maximal intrinsic activity, i.e. intrinsic activity observed in the presence of 100 nM DHT, was set at 1.00): ++ ≥0.80; + between 0.50 and 0.80; ± between 0.20 and 0.50; - <0.20

Claims

1. A compound having the formula



wherein

X is S, SO or SO_2;

R^1 is a 5-6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, (1C-4C)fluoroalkyl, nitro, (1C-4C)alkyl, (1C-4C)alkyloxy or (1C-4C)fluoroalkoxy;

R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, 2-pyridyl, 2-pyridyl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl;

R^3 is H, halogen or (1C-4C)alkyl;

R^4 is H, OH or halogen;

R^5 is H, OH, (1C-4C)alkoxy, NH_2, CN, halogen, (1C-4C)fluoroalkyl, NO_2, hydroxy(1C-4C)alkyl, CO_2H or

R^5 is NHR^6, wherein R^6 is (1C-6C)acyl optionally substituted with one or more halogens, or

R^5 is $C(O)N(R^8,R^9)$, wherein R^8 and R^9 each independently are H, (1C-6C)cycloalkyl, or

R^8 and R^9 form together with the N a heterocyclic 5-6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl, or

R^8 and R^9 each independently are CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)amino, (mono- or di(1C-4C)alkyl)aminocarbonyl, or a 5-6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring;

or a salt or hydrate form thereof.

2. A compound according to claim 1, characterised in that

R^1 is a 5-6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, CF_3, nitro, methoxy, trifluoromethoxy or methyl;

R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, 2-pyridyl, 2-pyridyl-N-oxide, benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl;

R^3 is H, halogen or (1C-2C)alkyl;

R^4 is H or F.

3. A compound according to claim 2, characterised in that

R^5 is H, (1C-4C)alkoxy, CN, Hal, (1C-4C)fluoroalkyl, NO_2, or

R^5 is NHR^6, wherein R^6 is (1C-6C)acyl optionally substituted with one or more halogens, or

R^5 is $C(O)N(R^8,R^9)$, wherein R^8 and R^9 each independently are H, (1C-6C)cycloalkyl, or

R^8 and R^9 form together with the N a heterocyclic 5-6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl, or

R^8 and R^9 each independently are CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)amino, (mono- or di(1C-4C)alkyl)-aminocarbonyl, or a 5-6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring.

4. A compound according to claim 3, characterised in that

R^3 is H or halogen;

R^4 is H;

R^5 is H, OH, (1C-4C)alkyloxy, CN, F, Cl, CF_3, NO_2, or

R^5 is NHR^6, wherein R^6 is (1C-3C)acyl optionally substituted with one or more halogens or

R^5 is $C(O)N(R^8,R^9)$, wherein R^8 and R^9 each independently are H, (1C-4C)cycloalkyl, or

R^8 and R^9 each independently are CH_2R^{10}, wherein R^{10} is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, (1C-2C)alkylester of carboxy(1C-2C)alkyl, (1C-3C)alkyloxy(1C-3C)alkyl), (1C-4C)cycloalkyl, (mono- or di(1C-

4C)alkyl)amino, (mono- or di(1C-4C)alkyl)aminocarbonyl, or a 5-membered heterocyclic ring.

5. A compound according to claim 4, characterised in that

X is S or SO_2.

R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-benzamide, 2-methoxyphenyl, 2-cyanophenyl or 2-pyridyl;

R^3 is H or F;

R^5 is H, OH, (1C-2C)alkyloxy, CN, F, Cl, CF_3, NO_2, or

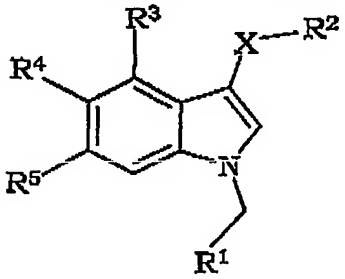
R^5 is NHR^6, wherein R^6 is acetyl or trifluoroacetyl, or

R^5 is $C(O)N(R^8,R^9)$, wherein R^8 is H and R^9 is H, cyclopropyl or

R^9 is CH_2R^{10}, wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, methoxy(1C-2C)alkyl, cyclopropyl.

Abstract

This invention provides non-steroidal compounds with affinity for the androgen receptor and utility for androgen-receptor related treatments, having a structure according to the formula



wherein X is S, SO or SO_2; R^1 is a 5-6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, (1C-4C)fluoroalkyl, nitro, (1C-4C)alkyl, (1C-4C)alkyloxy or (1C-4C)fluoroalkoxy; R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, 2-pyridyl, 2-pyridyl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl; R^3 is H, halogen or (1C-4C)alkyl; R^4 is H, OH or halogen; R^5 is H, OH, (1C-4C)alkoxy, NH_2, CN, halogen, (1C-4C)fluoroalkyl, NO_2, hydroxy(1C-4C)alkyl, CO_2H, NHR^6 or $C(O)N(R^8,R^9)$. Herein is R^6 (1C-6C)acyl optionally substituted with one or more halogens, and are R^8 and R^9 each independently H, (1C-6C)cycloalkyl, CH_2R^{10} or form together with the N a heterocyclic 5-6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl, where by R^{10} is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)amino, (mono- or di(1C-4C)alkyl)aminocarbonyl, or a 5-6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring.